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CORRELATION BETWEEN PROTHROMBIN TIME, ACTIVATED PARTIAL THROMBOPLASTIN TIME AND D – DIMER WITH PROGNOSIS OF ACUTE ISCHEMIC STROKE IN ADAM MALIK HOSPITAL MEDAN

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Abstract

Background: The state of hypercoagulation is the basis for thrombosis and significant for the occurrence of ischemic stroke. About 80% of ischemic strokes, the basis of which is atherothrombosis in large blood vessels, microateromes in small blood vessels, and emboli from the heart.
Objectives: To determine the relationship between prothrombin time, activated partial thromboplastin time and d-dimer with the prognosis of acute ischemic stroke.
Methods: This study uses a cross sectional design. Sampling was carried out at H. Adam Malik General Hospital Medan. The study sample was taken as many as 40 subjects consecutively. To determine the difference in prothrombin time (PT), activated partial thromboplastin time (APTT) and d-dimer levels and NIHSS scores paired t tests were used if the data were normally distributed and the Wilcoxon test if the data were not normally distributed. And determine the relationship between prothrombin time, activated partial thromboplastin time and d-dimer with NIHSS scores on the first and seventh days the Spearman correlation was used.
Results: Demographic characteristics of the subjects are the average age of 52-<68 years, the level of high school education, the work of housewives and farmers and the Batak tribe. There is no significant relationship between PT firts day and NIHSS score first day and there is no significant relationship between PT seventh day and NIHSS score seventh day. There is no significant relationship between APTT first day and NIHSS first day score and there is no significant relationship between APTT seventh day and NIHSS score seventh day. There is a significant relationship between D-dimer first day and NIHSS first day score and there is a significant relationship between D-dimer seventh day and NIHSS score seventh day.
Conclusions: There is a significant relationship between d-dimer with NIHSS scores on the first day and seventh days in patients with acute ischemic stroke.

Introduction

The hemostatic disorders that occur are associated with coagulopathy. The hypercoagulation state forms the basis of thrombosis and is significant for the onset of ischemic stroke. Approximately 80% of the incidence of ischemic stroke, the basis of occurrence is atherothrombosis in large blood vessels, microateromes in small blood vessels, and embolism from the heart.[1] Thrombotic formation of atherosclerotic plaques as activation of the extrinsic pathway of blood clotting. In his research, he found that intrinsic factor (factors V, VIII, IX, X, Xa) was also increased in the formation of thrombus from atherosclerotic lesions.[2]

Data in Indonesia, stroke is in the third position of the degenerative disease group after heart disease and malignancy. The prevalence of stroke (permil) based on the doctor's diagnosis is the highest in Indonesia, namely in the province of East Kalimantan at 14.7 ‰ and the lowest in Indonesia, namely in Papua at 4.1‰. The most prevalence of stroke at the age above 75 years and over is 50,2 ‰. Percent stroke prevalence in population aged ≥ 15 years based on doctor's diagnosis in 2018 was the highest for those who did not / had not attended school at 21.2 ‰.[3]

Stroke is an episode of neurological dysfunction caused by ischemia or hemorrhagic, lasts> 24 hours or dies, but does not have sufficient evidence to be classified.[4] Ischemic stroke is a clinical sign of dysfunction or damage to brain tissue caused by a lack of blood flow to the brain which disrupts the need for blood and oxygen in the brain tissue.[5] Ischemic stroke is the leading cause of death worldwide and the leading cause of disability in the United States. More than 8% of all deaths are associated with ischemic stroke.[6] In order to diagnose stroke cases, ideally it should be determined using 2 parallel paths, namely based on clinical observations of the characteristics of the

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syndrome / symptom set and the course of the disease; and pathophysiological characteristics and disease mechanisms confirmed by pathological, laboratory, electrophysiological, genetic, or radiological data.[7] CT-scan is a diagnostic support tool that uses X-ray imaging and has the ability to detect brain structures very well, is used in emergency cases and determines the stage of stroke.[8]

Arterial thrombosis occurs in many branching areas because there is a change in blood flow so that endothelial damage is easy. The loss of non-thrombogenic properties leads to activation of platelets and the blood clotting system resulting in thrombus.[9] Platelets release adenosine diphosphate (ADP) from solid granules and produce thromboxane A2 (TxA2). These substances stimulate other platelets that are still circulating to change shape and then stick together (aggregate). Aggregated platelets will release more ADP and TxA2 which will stimulate further aggregation.[10]

The National Institutes of Health Stroke Scale is a grading scale performed on stroke patients to see the progress of acute phase care outcomes. The NIHSS assessment was carried out twice, namely on the first day of admission and on discharge from treatment. Assessment of entry and exit can be used as a benchmark for successful treatment. The advantages of the NIHSS are that it can be done quickly, approximately 15 minutes, has been widely used and validated, is useful for acute stroke conditions, is easy to learn and the score is simple, the level of reability is high among score users.[11]

PT is the most commonly performed coagulation test. The reagents for PT are tissue thromboplastin and ionized calcium. These reagents will replace tissue factor for activating factor X in the presence of factor VII without platelets or intrinsic pathway procoagulants when added to citrate-containing plasma. To get normal PT results, plasma must contain at least 100 mg / dL of fibrinogen and adequate levels of factors VII, X, V, and prothrombin. PT prolongation as an isolated finding with aPTT normally occurs only in factor VII deficiency. PT and aPTT prolongation can occur for a variety of reasons, including multiple coagulation factor deficiency, oral anticoagulant therapy, liver disease, vitamin K deficiency, and deficiency of common pathway factors.[12]

aPTT is a medical test for blood clots. Normal aPTT timing requires the following coagulation factors: I, II, V, VIII, IX, X, XI, and XII. The dysregulation of the intrinsic pathway is expected to contribute to thromboembolic disease. There is a correlation between plasma levels of factors VIII, IX, and XI and the risk of venous thromboembolism. The activity factor XI which is more than the normal value is also a risk factor for stroke and ischemic attack in a retrospective analysis of patients younger than 55 years.

Shortening of aPTT is thought to detect hypercoagulation and has clinical relevance to an increased risk of thromboembolism. Shortening of aPTT was significantly associated with acute ischemic stroke and stroke severity.[13]

Several studies have shown that D-dimer levels are increased in the acute phase of ischemic stroke. Ischemic stroke is caused by a thrombus or embolus obstruction in the brain vascular. The thrombus is composed of fibrin along with platelets, Gp Ib, Gp IIb / IIIa, von willebrand factor and tissue factor (collagen). The presence of a thrombus that blocks blood flow makes the body perform homeostasis to destroy the thrombus. D-dimer is the end product of fibrin breakdown by plasmin. So the D-dimer examination will be very useful, either directly or indirectly, to determine the presence or breakdown of thrombus. It's just that this D-dimer examination cannot show the location of the thrombus.[14]

Method

Study samples

The study samples were taken from patients with acute ischemic stroke in Adam Malik General Hospital with a consecutive sampling technique. The study subjects consisted of 40 first ever stroke patients and were willing to participate in this study by signing a research-informed consent sheet.

Study design

This study used a cross-sectional design approach without treatment interventions. Patients who have been diagnosed with first ever ischemic stroke were examined for prothrombin time, activated partial thromboplastin time and d-dimer levels on the first and seventh day of the admission. Then the prognosis of stroke was assessed

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by calculating the National Institutes of Health Stroke Scale (NIHSS) score on the first and seventh day of admission.

Statistical analysis

Data from the study were analyzed statistically using the SPSS Windows computer program (Statistical Product and Science Service) version 25.0 to analyze the correlation between study variables, in this case, to determine the difference in prothrombin time, activated partial thromboplastin time and d-dimer levels and NIHSS scores were used paired t tests if the data were normally distributed and the Wilcoxon test if the data were not normally distributed. And to determine the relationship between prothrombin time, activated partial thromboplastin time and d-dimer with NIHSS scores on the first and seventh days the Spearman correlation was used.

Results

Acute ischemic stroke patient who received treatment at H. Adam Malik General Hospital Medan in Maret until June 2020, there were 40 subjects with acute ischemic stroke who participated in this study.

Based on the characteristics of 40 study subjects, the mean age of the study subjects is 59.90 ± 11.71 years old with the largest age range at the age of 52 - <68 years old as many as 22 subjects (55%) . The age range 36-<52 years old as many as 10 subjects (25%), age range 68-<84 years old as many as 6 subjects (15%), the oldest is ≥84 years old as many as 2 subjects (5%). The most gender of the subjects is a woman as many as 22 subjects (55%). The most educational level of the subjects is high school graduates as many as 23 subjects (57.5%). The most occupation of the subjects are housewives and farmers as many as 17 subjects (42.5%). For complete data about the characteristics of the study, subjects are shown in table 1 below.

Table 1. Demographic Characteristics of Study Subjects (n = 40)

Characteristics	Frequency n=40	Percentage (%)
Age, average ± SD (years)	59,90 ± 11.71	
- 36-<52 years old	10	25
- 52-<68 years old	22	55
- 68-<84 years old	6	15
- ≥ 84 years old	2	5
Sex		
- Male	18	45
- Female	22	55
Educational Level		
- Middle School	12	30
- High School	23	57.5
- University	5	12.5
Occupation		
- Housewive	17	42.5
- Farmer	17	42.5
- Retired	2	5
- Private employee	2	5
-Labor	1	2.5
-Lecturer	1	2.5

The results of descriptive analysis in this study, the value of PT first day and seventh day using the mean ± SD value because the data is normally distributed, the PT first day value was 15.74 ± 2.76 seconds and the PT seventh day value was 14.77 ± 2.87 seconds. Meanwhile, the APTT and D-dimer values in this study used the median (minimum-maximum) value because the data were not normally distributed. Obtained APTT first day value is 29.05 (20.60-60.50) seconds, the APTT seventh day value is 28.10 (19.50-58.50) seconds. The D-dimer first day value is 625 (100-4000)ng/ml, the D-dimer seventh day value is 650 (100-3980) ng/ml. For complete data regarding the characteristics of Prothrombin Time, Activated Partial Thromboplastin Time and D-dimer are presented in table 2 below this.

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Table 2. Characteristics of Prothrombin Time, Activated Partial Thromboplastin Time and D-dimer

	First day	Seventh day
PT*	15.74±2.76	14.77±2.87
APTT**	29.05 (20.60–60.50)	28,10 (19.50–58.50)
D – dimer**	625 (100–4000)	650 (100–3980)

*Data is presented in the form of mean and standard deviation (data normally distributed)
**Data is presented in the form of median and minimum-maximum value (data is not normally distributed)

The descriptive analysis of the characteristics of the NIHSS score in this study used the median (minimum-maximum) value because the data were not normally distributed. The NIHSS first day value was 4 (2-30), with the most characteristic neurological deficit in the mild category, as many as 23 subjects (57.5%). The NIHSS seventh day value was 4 (2-30), with the most characteristic neurological deficit in the mild category as many as 26 subjects (65%). This can be seen in table 3 below this.

Table 3. Characteristics of the NIHSS Score

Characteristics Score	Median (minimum-maksimum)	Frequency (40)	Percentage (%)
NIHSS Score first day	4		
• Mild	(2-30)	23	57.5
• Moderate		9	22.5
• Severe		3	7.5
• Very Severe		5	12.5
NIHSS score seventh day	4		
• Mild	(2-30)	26	65
• Moderate		6	15
• Severe		3	7.5
• Very Severe		5	12.5

Data are presented in the form of median and minimum-maximum values (data are not normally distributed)

In this study, the mean value of PT first day was 15.74 ± 2.76 while PT seventh day was 14.77 ± 2.87. And there is a significant mean difference between PT first day and seventh day (p <0.001). The APTT first day value was 29.05 (20.60-60.50) while the APTT seventh day value was 28.10 (19.50-58.50). And there is a significant difference between APTT first day and seventh day (p <0.001). The value of D - dimer first day 625 (100 - 4000) while D - dimer seventh day 650 (100-3980). And there is a significant difference between D-dimer first day and seventh day (0.001). The NIHSS first day value is 4 (2-30) while the NIHSS seventh day value is 4 (2-30). And there is a significant difference between NIHSS first day and seventh day (p = 0.002). This can be seen in table 4 below.

Table 4. Difference between Prothrombin Time, Activated Partial Thromboplastin Time, D-dimer and NIHSS scores on the first and seventh day

	First day	Seventh day	P
PT*	15.74±2.76	14.77±2.87	< 0.001
APTT**	29.05 (20.60 – 60.50)	28.10 (19.50 – 58.50)	< 0.001
D – dimer**	625 (100 – 4000)	650 (100 – 3980)	0.001
NIHSS**	4 (2 – 30)	4 (2 – 30)	0.002

***Paired T test**
****Wilcoxon**

In this study, the Spearman test was carried out on 40 research subjects, it was found that there was no significant relationship between PT and NIHSS score on first day with p=0.081 and had a weak correlation strength (r = 0.279). There was no significant relationship between PT and NIHSS score on seventh day with p =0.088 and

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has a weak correlation strength (r = 0.273). There was no significant relationship between APTT and NIHSS scores on first day with p=0.488 and had a weak correlation strength (r = -0.113). There was no significant relationship between APTT and NIHSS scores on seventh day with p=0.268. and has a weak correlation strength (r = -0.179). There was a significant relationship between D-dimer and NIHSS score on first day with p <0.001 and had a very strong correlation strength (r = 0.915). There was a significant relationship between D-dimer and NIHSS score on seventh day with p <0.001 and has a very strong correlation strength (r = 0.904).

Table 5. Correlation between Prothrombin Time, Activated Partial Thromboplastin Time, D-dimer and NIHSS score in acute ischemic stroke patients

Analysis	First day		Seventh day	
	R	*p*	***R***	*p*
PT between NIHSS	0,279	0,081	0,273	0,088
APTT between NIHSS	-0,113	0,488	-0,179	0,268
D-dimer between NIHSS	0,915	<0,001	0,904	<0,001

Spearman Test

Discussions

The average age characteristics of acute ischemic stroke patients in this study are relevant to the previous study which conducted by Rambe et al (2013) which stated that the mean age of stroke patients was 59 years (age range 20-95 years) and the highest number of subjects was 40-59 years old.[15] In a study conducted by Lona et al (2019), it was found that the most subjects were in the age group >50 - 60 years as many as 23 people (50%).[16] Goldstein et al (2011) mentioned that the cumulative effect of aging on the cardiovascular system and the progressive development of stroke risk factors over a period of time increase the risk of developing a stroke. Stroke risk doubles after age 55.[17] Reilly (2018) mentioned that stroke is a disease of aging, which occurs most often at age above 65 years old. The most sex characteristics of acute ischemic stroke patients in this study are women as many as 22 subjects (55%) more than men as many as 18 subjects (45%).[18] The results of this study are relevant with research conducted by Rambe et al (2013) showing that the demographic characteristics of women are more, namely 52.7% compared to men.[15] Reilly (2018) mentioned that women have several unique risk factors that differ from men, including use of oral contraceptives, pregnancy, menopause and hormone replacement therapy. Although the incidence of stroke is low in women of reproductive age, the use of oral contraceptives with high levels of the hormone estrogen can increase the risk of ischemic stroke.[18] The characteristics of the educational level of the research subjects in this study are senior high school as many as 23 subjects (57.5%). The occupational status of the most respondents are housewives and farmers, respectively 17 subjects (42.5%) and the lowest are laborers and lecturers as many as 1 subject (2.5%). The results of this study are relevant to previous research conducted by Kusumawardani (2011) at dr. Kariadi Semarang Hospital who received the most education for stroke sufferers was high school, amounting to 52.4%.[19] According to Riskesdas (2013), the prevalence of stroke tended to be higher in people with low levels of education based on diagnosis of health services or symptoms as much as 32.8%.[3] According to Kabi (2015) at DR. R. D. Kandou Manado General Hospital found that the most ischemic stroke patients were housewives at 30%. Respondents' ethnicity are divided into Batak as many as 14 subjects (35%), Javanese as many as 13 subjects (32.5%) and Karo as many as 13 subjects (32.5%), so it can be concluded that most of the respondents with ischemic stroke came from the Batak tribe.[20] This is in accordance with the research of Rambe et al (2013) in the ischemic stroke group that was found as many as 40.7% of the Batak tribe.[15] Another relevant research result was conducted by El harizah et al (2016) on 100 stroke patients at the neurology polyclinic and the inpatient room of the USU FK / RSUP. H. Adam Malik Medan in the period December 2015 to April 2016, it was found that the most people suffering from stroke were the Batak tribe with 63 patients (63%).[21] In a study conducted by Lona (2019), the highest number of respondents was the Batak ethnic group as many as 33 subjects (71.7%).[16] Sjahrir (2003) mentioned that the cause of the high incidence of stroke in the Batak tribe compared to the non-Batak tribe may be due to non-modifiable risk factors, namely genetically and modifiable stroke risk factors.[5] Nainggolan et al (2015) mentioned that the Batak tribe has the characteristic of eating more than other tribes so that it is more likely to be obese.[22] Manurung et al (2015) mentioned that Batak specialties also contain lots of cholesterol levels.[23] In the Tambunan (2019), it was found that stroke patients were more common in the Batak tribe, which was 64.2% compared to non-Batak.[24]

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Characteristics of Prothrombin Time, Activated Partial Thromboplastin Time and D-dimers in this study, PT value on first day was 15.74 ± 2.76 seconds, the PT value on seventh day was 14.77 ± 2.87 seconds. APTT value on first day was 29.05 (20.60-60.50) seconds, APTT value on seventh daywas 28.10 (19.50-58.50) seconds. The D-dimer value on first day was 625 (100-4000) ng / ml, the D-dimer value on seventh day is 650 (100-3980) ng / ml. This is relevant with the results of research by Zi et al(2014) obtained that the mean value of PT was 12.3 (11.2-13.1) seconds and the mean APTT value was 28.3 (25.9-30.2) seconds and mean the D-dimer value is 880 (280-2110) ng / ml.[25] And the APTT value is relevant to study by Lin et al(2015), the mean APTT value was 27.6 ± 2.4 seconds in acute ischemic stroke patients.[13] The study of Yao et al (2019), it was found that the mean D-dimer value was 560 (240-1790) ng / ml.[26] The study of Darmawaty et al (2011) in acute ischemic stroke patients, the mean D-dimer on the first day was 1230 ± 890 and the mean D-dimer on the seventh day was 1330 ± 840. Increased D-dimer as a marker of coagulation and fibrinolysis reflects thrombus formation and breakdown. The higher the D-dimer level, the more thrombus is formed.[27] In Zhang (2017), an increase in D-dimer levels indicated that more fibrin threads were formed and could increase the incidence of thrombosis. The reason for the increase in D-dimer, the risk of ischemic stroke is not clear. D-dimer levels can be a marker of hypercoagulation which can cause the formation of fibrin to form thrombus. High D-dimer levels could be a sign for the occurrence of ischemic strokes, especially cardioembolic strokes.[28]

Characteristics score NIHSS (National Institute Health Stroke Scale) in this study, the NIHSS score on first day was 4 (2-30), with the most characteristic neurological deficit in the mild category, as many as 23 subjects (57.5%). The NIHSS value on seventh day was 4 (2-30), with the most characteristic neurological deficit in the mild category as many as 26 subjects (65%). Study based on Yao et al (2019), the mean NIHSS score was 5 (3-8). It means that study in the moderate category. This can happen because Yao's research not only involved D-dimer levels, but there are other factors such as dyslipidemia, drinking alcohol, having hypertension and diabetes mellitus were included in the study. So that the average NIHSS score in Yao's study was higher than this study.[26]

Difference between prothrombin time, activated partial thromboplastin time, D-dimer and NIHSS scores on first day and seventh day in this study, there was a significant mean difference between PT on first and seventh day ($p < 0.001$), APTT on first and seventh day ($p < 0.001$), D-dimer on first and seventh day ($p = 0.001$) and NIHSS score on first and seventh day ($p = 0.002$). In the study of Zakiah et al (2018) in acute ischemic stroke patients, there was a significant difference in the mean value of D-dimer on the first day and the seventh day with p of 0.011 ($p < 0.05$). This can be due to differences in the assessment of each measurement of clinical appearance.[29]

Correlation between prothrombin time, activated partial thromboplastin time, D-dimer and prognosis of acute ischemic stroke in this study, based on the statistical analysis of the Spearman test on 40 subjects, it was found that there was no significant relationship between the PT value and the NIHSS score on first day ($p=0.081$) and had a weak correlation strength ($r = 0.279$). There is a significant relationship between PT and NIHSS score on seventh day ($p=0.088$) and has a weak correlation strength ($r = 0.273$). There was a negative correlation between APTT and NIHSS score on first day ($p=0.488$) and had a weak correlation strength ($r = -0.113$). There was a negative correlation between APTT and NIHSS score on seventh day ($p=0.268$) and had a weak correlation strength ($r = -0.179$). There was a significant relationship between D-dimer and NIHSS score on first day ($p < 0.001$) and had a very strong correlation strength ($r = 0.915$), there was a significant relationship between D-dimer and NIHSS score on seventh day ($p < 0.001$) and has a very strong correlation strength ($r = 0.904$). According to Kravchenko (2018), it was found that the PT value was more than 19 seconds in 29 patients (45.5%) of ischemic stroke patients ($p = 0.466$) and an APTT value of more than 45 seconds for 26 patients (40.5%) ($p = 0.224$). According to Yao et al. (2019), increased plasma D-dimer levels have a very significant relationship with the incidence of acute ischemic stroke. And plasma D-dimer levels are a convenient and economical indicator that can be used to improve the management of stroke rehabilitation and ischemic stroke outcome.[30] In the study of Lin et al (2015) shortened APTT has a significant relationship with acute ischemic stroke. Shortened APTT was also associated with the incidence of acute ischemic stroke and stroke severity. And it included other risk factors such as smoking, diabetes mellitus, hypertension, coronary heart disease, acute myocardial infarction and other contributing factors. Where the factors as mentioned above can influence hypercoagulation, resulting in dysregulation of intrinsic factor which causes shortening of the APTT.[13,26]

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Conclusion

There is a significant relationship between d-dimer with NIHSS scores on the first day and seventh days in patients with acute ischemic stroke.

Suggestion

This study has limitations, namely before the seventh day there were some patients who had gone home for outpatient treatment because their general condition had improved so that the implementation of this study took longer.

References

[1] Setiabudy, R.D., 2007. Pathophysiology of Thrombosis. In Rahajuningsih D Setiabudy (editor). Hemostasis and Thrombosis.3rd Edition. Balai Penerbit Faculty of Medicine, University of Indonesia. Jakarta.
[2] Natalya, M.A., Diana, V.K., Shima, M., and Saenko, L.E. 2002. Intrinsic Pathway of Blood Coagulation Contributes to Thrombogenicity of Atherosklerotic Plaque. Department of Biochemistry. USA. p: 4475-4485.
[3] Riset Kesehatan Dasar (Riskesdas). 2018. Health Research and Development Agency of the Ministry of Health Indonesia.
[4] Sacco, R. L., Kasner, S. E., Broderick, J. P., Caplan, L. R., Culebras, A., Elkind, M., et al. 2013. An Update Definition of Stroke for 21st Century: Professionals from The American Association/ American Stroke Association. Stroke. 40: 2064-2089.
[5] Sjahrir. 2003. Ischemic Stroke. Yandira Agung. Medan.
[6] Lucke, B.P., Turner, R.C., Logsdon, A.F., and Nguyen. 2014. Metabolic Syndrome and Its Profound Effect on Prevalence of Ischemic Stroke. AMSRJ. p: 29-38.
[7] Kidwell, S. C., and Warach, S. 2003. Acute Ischemic Cerebrovascular Syndrome Stroke. Department of Neurology University of California. Los Angeles. p: 2995 - 2998.
[8] Browaeys, P., Binaghi, S., and Meuli, R.A., 2006. Multislice ComputedTomography in Acute Stroke. In: Knollmann F, Coakley FV, editors. Multislice CT: principles and protocols. Philadelphia: Saunders Elsevier. p: 1-16.
[9] Rahajuningsih, D. S., 2009. Pathophysiology of Thrombosis in Hemostasis and Thrombosis Fourth Edition. Faculty of Medicine, University of Indonesia. Jakarta.
[10] Ross, and Epstein, H., 2009. Artherosclerosis and Inflammatory Disease. The New England Journal of Medicine Volume 340 Number 2.. p: 115-126.
[11] Soertidewi, L. 2011. Monitoring Stroke Scale: Misbach, J., Soertidewi L., Jannis, J., editor. Diagnostic Aspects, Pathophysiology, Management. p: 301-315. Publishing Agency Faculty of Medicine, University of Indonesia. Jakarta.
[12] Ronald, A. and Sacher 2012. Clinical Review of Laboratory Examination Results. Edition 11. EGC. Jakarta.
[13] Lin, H. C., Kuo, W. Y., and Kuo, Y. C. 2015. Shortened Activated Partial Thromboplastin Time Is Associated With Acute Ischemic Stroke, Stroke Severity, and Neurological Worsening. National Stroke Association. Taiwan. p: 2270 – 2276.
[14] Haapaniemi, E., and Tatlisumak, T., 2009. Is D-dimer Helpful in Evaluating Stroke Patients Department of Neurology Helsinki University. Finland. 141-150.
[15] Rambe, A. S., Fithrie, A., Nasution, I., dan Tonam. 2013. Profile of Stroke Patients at 25 Hospitals in North Sumatra 2012, Hospital Based Survey. Neurona. 30(2).
[16] Lona, A., Arina, C. A. and Rambe, A. S. 2019. Relationship Between Paco2 Levels And Clinical Outcomes Of Acute Ischemic Stroke Patients With Decreased Of Consciousness. International Journal Of Research Science & Management. Medan. 6(12): 1-7.
[17] Goldstein, L.B., Cheryl, D.B., Robert, J.A., Lawrence, J.A., Lynne, T.B., Seemant, C., et al. 2011, Guidelines for the Primary Prevention of Stroke: A Guideline for Healthcare Professional From the American Heart Association/American Stroke Association, *Stroke*, 42:517.
[18] Reilly, M. R. and McCullough, L. D. 2018. Age and Sex Are Critical Factors in Ischemic Stroke Pathology. Endocrinology. 159(8): 3120-31.
[19] Kusumawardani, dan Risi, P. 2011. Contribution of Hypertension to Atherosclerosis of Internal Carotid Artery in Ischemic Stroke Patients [Tesis].Diponegoro University, Semarang.

[20] Kabi, G., Tumewah, R., dan Kembuan, M. 2015. Description of Risk Factors in Patients with Ischemic Stroke Hospitalized in Neurology, RSUP prof. Dr. R. D. Kandou manado July 2012 - June 2013. Sam Ratulangi University Manado. Jurnal E- Clinic. P:457-462.

[21] El-Harizah, Q., Chan D. D., dan Nasution, I. 2016. Risk Factors for Hypertension, Dyslipidemia, Smoking, Gout, Obesity, Diabetes Mellitus, and Family History of Stroke Patients. Downloaded on May 22, 2020 from http://repository.usu.ac.id/bitstream/handle/123456789/654 52/ Abstract.pdf?sequence=6&isAllowed=y

[22] Nainggolan, T., Pasaribu, J. B., Simanjuntak, M. S. E., dan Simorangkir, M. S. E. 2015. Batak characters: Past, Present, and Future. Pustaka Obor Indonesia Foundation:Jakarta.

[23] Manurung, M., Diani, N. dan Agianto. 2015. Analysis of Stroke Risk Factors in Stroke Patients in Hospital Banjarbaru. Jurnal DK. 3(1):74-85.

[24] Tambunan, L. P. S., Arina, C. A. dan Sjahrir, H. 2018. The Difference of Stroke Risk Factors Between Batak and Non-Batak Tribe in H. Adam Malik Hospital Medan. USU's Institutional Repository. p. 103-131.

[25] Zi, W. J., and Shuai, J. Plasma D-Dimer Levels Are Associated with Stroke Subtypes and Infarction Volume in Patients with Acute Ischemic Stroke. Department of Neurology, Xin Qiao Hospital, Third Military Medical University, Chongqing, P. R. China.

[26] Yao, T., Tian, L. B., and Li, G. 2019. Elevated Plasma D-dimer Levels are Associated with Short Term Poor Outcome in Patients with Acute Ischemic Stroke: a Prospective, Observational Study. BMC Neurology. 19: 2-8.

[27] Darmawaty., Arif, M., Pakasi, R., Hardjoeno., Bahar, B., dan Muis, A. 2011. Hubungan Kadar D – dimer dengan Skor Canadian Neurological Scale (CNS) pada Penderita Stroke Iskemik Akut [Tesis]. UNHAS, Makassar.

[28] Zhang, J., Song, Y., Shan, B., He, M., Ren, Q., Zeng, Y., et al. 2017. Elevated Level of D – dimer Increases The Risk of Stroke in Impact Journal. Department of Neurosurgery Sichuan University. China. p: 2208 – 2219.

[29] Zakiah, N. A., Handayani, dan S., Rambe, S. A. 2018. Relationship between D-dimer levels on the first day of hospital admission and the seventh day of clinical presentation in patients with acute ischemic stroke. Nusantara Medicine Magazine Volume 51. p: 87-90.

[30] Kravchenko, O., Melnyk, V., Tsarenko, T., Kostiuk, O., Halenova, T., Raksha, N, et al. 2008. The Blood Coagulation Tests From Ischemic Stroke Patients With or Without Type 2 Diabetes Mellitus in Biomedical Research. Department of Neurology Bogomolets National Medical University. Ukraine. 2938 – 2943.